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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,692	09/23/2003	Thomas Jeffrey Clark	T103 1470.2	4313

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EXAMINER	
HABTE, KAHSAY	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/668,692	CLARK ET AL.	
	Examiner	Art Unit	
	Kahsay Habte, Ph. D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *8-10* is/are allowed.

6)☒ Claim(s) *1-7 and 11-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/11/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-60 are pending.

Election/Restrictions

2. Applicant's election of Group I that is drawn to azabicyclo[2.2.1]compounds in the reply filed on 10/12/2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. It is recommended that applicants limit their invention to Group I that is drawn to azabicyclo[2.2.1]compounds. This can be done by requiring either **p** or **q** to be exactly 1. Note that the structure contains 7-memberd does not limit the invention, since azabicyclo[3.1.1]compounds also give a 7-membered structure.

Objection

4. Claims 2-6, 8-10, 20, 22-26, 28-30, 40, 42-46, 48-50, and 60 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In claims 1, 21, and 41, "Cy" represents a 5 or 6 member aromatic ring, but in claims 2-6, 8-10, 20, 22-26, 28-30, 40, 42-46, and 48-50, "Cy" is

substituted by A and A' which is broader than claims 1, 21, or 41 in that those claims do not permit substitution.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There has been recited a method for treating a disorder characterized by an alteration in normal neurotransmitter release. Applicants recited "neurotransmitter" in general, but neurotransmitters are extremely broad and in nature.

A neurotransmitter is a chemical that transmits information across the junction (synapse) that separates one nerve cell (neuron) from another nerve cell or a muscle and is stored in the nerve cell's bulbous end (axon). When an electrical impulse traveling along the nerve reaches the axon, the neurotransmitter is released and travels across the synapse, either prompting or inhibiting continued electrical impulses along the nerve. There are more than 300 known neurotransmitters, including chemicals such as acetylcholine, norepinephrine, adenosine triphosphate, Serotonin (5-HT), Histamine; amino acids such as GABA, Glycine, Glutmate, and Asparate; neuroactive peptides such as bradykinin, endorphin, gastrin, neuropeptide Y, substance

P, etc. Neurotransmitters transmit information within the brain and from the brain to all the parts of the body. Abnormalities in the production or functioning of certain neurotransmitters have been implicated in a number of diseases, such as Alzheimer's disease, Parkinson's, and other disorders. The actions of some drugs mimic those of naturally occurring neurotransmitters.

For example, Acetylcholine is released at the synaptic ends of nerve fibers in the sympathetic and parasympathetic nervous systems and results in transmission of nerve impulses that contract or dilate muscles. It also increases stomach peristalsis, urinary tract contractions; and voluntary voiding pressure on the bladder. Acetylcholine releasing neurons in the pons are very active in REM sleep (dreaming), learning and memory are blocked by drugs which impair the synthesis and release of acetylcholine, and in certain cases choline (an amino acid necessary for the synthesis of acetylcholine) has been found to improve learning and memory. Alzheimer's Disease is associated with a 90% loss in the brain's production of the neurotransmitter acetylcholine in the basal forebrain and hippocampus.

Dopamine is a neurotransmitter that inhibits the transmission of nerve impulses--in the substantia nigra, basal ganglia, and corpus striatum of the brain. It is controlled by the enzyme Monamine Oxidase (MAO-B) that inhibits its production. Dopamine (DA) is involved in many behaviors; for example cocaine, opiates, and alcohol produce rewarding effects in part due to their abilities to promote the release of dopamine. Parkinson's Disease (PD) is accompanied by a selective destruction of dopamine neurons in the substantia nigra of the midbrain which send their axon terminals to the

striatum which is involved in motor control. PD is treated with L-dopa which is a precursor for the production of dopamine in the brain. Schizophrenia is treated with drugs, which block the binding of dopamine to its postsynaptic receptor sites. The better the drug is at blocking dopamine, the better it is at reducing the schizophrenia. The dopamine hypothesis of schizophrenia is that there is excessive dopamine stimulation in the frontal lobe due to a combination of genes and some as yet unknown aspect of the environment such as a perinatal virus or toxin.

Serotonin is a neurotransmitter arising from emotional stimuli of the limbic system. It is formed from tryptophan and found in animal and human tissue, especially the brain, blood serum, and gastric mucous membranes, and active in vasoconstriction, stimulation of the smooth muscles, transmission of impulses between nerve cells, and regulation of cyclic body processes. Low levels are associated with depression that seems to be relieved by Prozac type chemicals that act as serotonin uptake blockers. Serotonin (5HT) is involved in many behaviors; as examples: Human mood disorders (depressions) are effectively treated with drugs which specifically block the reuptake of serotonin into the presynaptic

axon terminal, for example fluoxetine (Prozac). The resultant enhanced serotonin activation brings about a cascade of events ultimately resulting in a reduced sensitivity of presynaptic autoreceptors for serotonin and reduced serotonin synthesis. This suggests that neurotransmitter dysregulation may be involved in depressive disorders.

Human OCD (Obsessive Compulsive Disorder) is effectively treated by serotonin reuptake inhibitors suggesting that this condition may also be due to dysregulation in serotonin synapses.

GABA (gamma-aminobutyric acid), is the main inhibitory neurotransmitter in the brain. Its actions, which are anxiety reduction, are mediated by the entry of chloride into a cell when GABA binds to its postsynaptic receptor site. Drugs such as Valium which act as anxiolytics (anti-anxiety) produce their effects by enhancing the effects of GABA at the synapse. The brain produces substances which enhance anxiety (beta-carbolines) as well as substances which reduce anxiety (e.g. allopregnanolone). All of these substances seem to modify the GABA receptor in the brain to produce their effects.

Glutamate is the main excitatory neurotransmitter in the brain. Its actions are mediated at two types of receptor sites (NMDA and AMPA). At the NMDA receptor glutamate binding will cause calcium to flow into a neuron (but only in large amounts when the AMPA receptors are also activated). These receptors are involved in the process of memory formation in the brain. Curiously, glutamate is also involved in a "suicidal" response when the brain is damaged such as in a stroke. Excess glutamate is neurotoxic and neurons are killed by the excessive calcium which enters the cell due to glutamate binding. It is glutamate which is produced excessively in ALS (Lou Gherig's Disease) and which causes the death of neurons in the spinal cord and brainstem.

As it is shown above, the neurotransmitters are extremely varied in nature, some are chemicals, gases, aminoacids, and peptides, they are associated with different

disorders. To this day, there is no single compound that can be used as in general to affect neurotransmitter release. Note that alteration covers increase and decrease of amounts and timing of all known neurotransmitters. Claims must be limited to what these compounds actually can do.

6. Claims 1-7, 11-14, 18-27, 31-34, 38-47, 51-54 and 58-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It has been recited in claim 1, 21 and 41, the phrase "B' is alkyenic", but there is no descriptive support for said phrase in the specification.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 and 11-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a. Claim 1 and claims dependent thereon are rejected because the term "substituted" in claim1 or elsewhere in the claims is indefinite. In the absence of the

specific moieties intended to effectuate modification by the "substitution" or attachment to the chemical core claimed, the term "substituted" renders the claims in which it appears indefinite in all occurrences wherein applicants fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties applicants regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed.

b. In claim 1, 21, and 41 the phrase, "B' is alkylenic" is indefinite. What is covered and what is not? What is it? Note that "B' is ethylenic" (-CH=CH-) has been recited in said claims that is specific example of alkylenic (see page 5 of the specification). It is recommended that applicants delete "alkylenic" from the claims, since there is no support in the specification for the broader claim language i.e. "B is alkylenic".

Like wise, the phrase "acetylenic" is indefinite. What is covered and what is not?

c. In claims 17, 37, and 57 the phrase "B' is a two carbon atom bridging species" is unclear. Is this referring to the carbon atoms than have been recited in claims 1, 21 and 41? If yes, are the two carbon atoms both part of the bridge i.e. –CH=CH- (both carbons required to be in the bridge itself) or is it permitted that only one of the two carbons atoms are involved in the bridging i.e. –C=(CH)-? If not, what species are included and what are not?

d. In claim 1, 21, and 41 the phrase "Z_j represents...j is an integer" is incorrect. The cases "J" (upper) and "j" (lower case) are inconsistent.

e. In claim 21, it has been recited a method for treating a disorder characterized by an alternation in normal neurotransmitter release. The scope of claim 21 is unknown. Which diseases are these? Determining whether a given disease responds or does not respond to such mediator will surely involve undue experimentation. Suppose that a given mediator X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many

different mediators must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

Note that there are more than 300 known neurotransmitters, thus, this should be repeated for each neurotransmitter.

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on (571) 272-0674, if there is no reply within 24 hours, James Wilson (Acting SPE) can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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KH
October 19, 2004